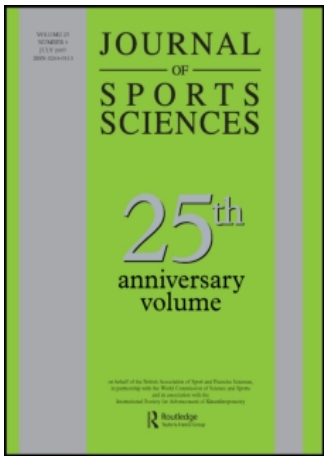

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The brain and fatigue: New opportunities for nutritional interventions?

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Abstract
It is clear that the cause of fatigue is complex, influenced by events occurring in both the periphery and the central nervous system. Work conducted over the last 20 years has focused on the role of brain serotonin and catecholamines in the development of fatigue, and the possibility that manipulation of neurotransmitter precursors may delay the onset of fatigue. While there is some evidence that branched-chain amino acid and tyrosine ingestion can influence perceived exertion and some measures of mental performance, the results of several apparently well-controlled laboratory studies have not demonstrated a positive effect on exercise capacity or performance under temperate conditions. As football is highly reliant upon the successful execution of motor skills and tactics, the possibility that amino acid ingestion may help to attenuate a loss in cognitive function during the later stages of a game would be desirable, even in the absence of no apparent benefit to physical performance. There are several reports of enhanced performance of high-intensity intermittent exercise with carbohydrate ingestion, but at present it is difficult to separate the peripheral effects from any potential impact on the central nervous system. The possibility that changes in central neurotransmission play a role in the aetiology of fatigue when exercise is performed in high ambient temperatures has recently been examined, although the significance of this in relation to the pattern of activity associated with football has yet to be determined.

Keywords: *Branched-chain amino acids, carbohydrate, dopamine, neurotransmission, serotonin, tyrosine*

Introduction

Progressive fatigue that occurs during high-intensity intermittent exercise, characteristic of many team sports including football, has been typically ascribed to the depletion of muscle glycogen, reductions in circulating blood glucose, hyperthermia, and the progressive loss of body fluids (Mohr, Krustrup, & Bangsbo, 2005). These factors are thought to result in distances covered, and the number and intensity of sprints undertaken by players, towards the end of the second half of play (Mohr, Krustrup, & Bangsbo, 2003). Although the idea that the central nervous system (CNS) is involved in feelings of tiredness, lethargy, and mood disturbances is not new, evidence has accumulated over the past 20 years to support a significant role of the brain in the aetiology of fatigue during strenuous exercise. It is now acknowledged that the cause of fatigue is a complex phenomenon influenced by both events occurring in the periphery and the CNS (Meeusen & De Meirleir, 1995; Nybo & Secher, 2004).

At the highest level, footballers have been reported to cover distances in excess of 10 km during competitive matches (Bangsbo, Norregaard, & Thorsoe, 1991). This activity typically consists of periods of walking and low- to moderate-intensity running, interspersed with explosive bursts of activity including sprinting, jumping, changes in speed and direction, and tackling. In many skill-based sports, participants have simultaneously to undertake mechanical work, often with a great physical demand, coupled with the precise performance of decisional and/or perceptual tasks. Football matches include periods of high-intensity activity, and successful football performance depends upon many factors, including technical, tactical, physical, physiological, and mental skills. Increased fatigue has commonly been observed after exercise and, although detrimental effects on mood or mental performance are typically small (Collardeau, Brisswalter, Vercruyssen, Audiffren, & Goubault, 2001), in sports such as football even minor decrements in mental

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performance can significantly influence the outcome of a game.

In this review, we discuss possible neurobiological mechanisms of fatigue and examine whether nutritional and pharmacological interventions to alter central neurotransmission are capable of influencing the development of fatigue during exercise.

The ''central fatigue hypothesis''

The ''central fatigue hypothesis'' is based on the assumption that during prolonged exercise the synthesis and metabolism of central monoamines, in particular serotonin, dopamine, and noradrenaline, are influenced. It was first suggested by Newsholme, Ackworth and Blomstrand (1987) that prolonged exercise results in an increase in brain serotonergic activity that may augment lethargy, cause an altered sensation of effort, perhaps a differing tolerance of pain/discomfort, and a loss of drive and motivation, thus limiting physical and mental performance.

The rate of serotonin synthesis is largely dependent upon the peripheral availability of the essential amino acid tryptophan. An increase in the delivery of trypyophan to the CNS will increase serotonergic activity because the rate-limiting enzyme, tryptophan hydroxylase, is not saturated under physiological conditions. Furthermore, free tryptophan and the branched-chained amino acids share the same carrier in order to pass across the blood–brain barrier, meaning that the plasma concentration ratio of free trypyophan to branched-chain amino acids is thought to be an important determinant of serotonin synthesis.

The underlying mechanisms behind the central fatigue hypothesis as proposed by Newsholme *et al.* (1987) can be divided into two interrelated parts:

1. Under resting conditions, most tryptophan, the precursor of serotonin, circulates in the blood loosely bound to albumin, a transporter shared with free fatty acids (FFA). The shift in substrate mobilization that occurs as exercise progresses causes an increase in plasma FFA concentration. This displaces tryptophan from binding sites on albumin, leading to a marked increase in free tryptophan. Free tryptophan is then readily available for transport across the blood–brain barrier.
2. Plasma branched-chain amino acid concentrations either fall or are unchanged during prolonged exercise. Since free tryptophan and branched-chain amino acids share a common transporter across the blood–brain barrier, a reduction in competing large neutral amino acids (LNAA) would increase the uptake of tryptophan into the CNS. The resulting elevation in tryptophan delivery results in an increased central synthesis of serotonin.

Is there experimental evidence for central fatigue?

Since neurotransmitters, including serotonin, dopamine, and noradrenaline, have been implicated in the aetiology of a wide variety of psychiatric and mood disorders (e.g. depression, anxiety disorders, Parkinson's disease), a vast number of drugs have been developed to directly manipulate central neurotransmission. Through an understanding of the action of these pharmacological agents, it has been possible to examine the role of the CNS in the fatigue process. However, at present there appears to be no published reports of the effects of pharmacological manipulation of central neurotransmission on performance during high-intensity intermittent activity.

Bailey and co-workers were among the first to examine the effects of pharmacological manipulation of brain serotonin concentrations through the administration of specific serotonin agonists and antagonists to rodents (Bailey, Davis, & Ahlborn, 1992, 1993). This early work provided good evidence for a role of serotonin in the development of fatigue, with a dose-dependent reduction in exercise capacity reported when central serotonin activity was augmented by the acute administration of a general serotonin agonist (Bailey *et al.*, 1992). Brain serotonin and dopamine content progressively increased during exercise, but at the point of exhaustion a marked fall in tissue dopamine content was apparent. Furthermore, exercise capacity was enhanced by a serotonin antagonist (LY-53857), although this was apparent only when the highest dose was administered (Bailey *et al.*, 1993).

Selective serotonin reuptake inhibitors (SSRIs)

The SSRIs are a class of drugs that selectively inhibit the reuptake of serotonin into the pre-synaptic nerve terminal, thus increasing the extracellular concentration of serotonin present at the post-synaptic receptors. These agents have been widely administered in the treatment of various psychiatric disorders, in particular depression, and were the first to be employed in the study of central fatigue. To date, three studies have investigated the effects of an acute dose of paroxetine (Paxil, Seroxat), with two reporting a reduction in exercise time to exhaustion (Struder *et al.*, 1998; Wilson & Maughan, 1992). A number of subsequent studies have examined the effects of pharmacological agents acting on central serotonergic neurotransmission during prolonged exercise, with largely negative results, making it

difficult at this stage to make a firm decision regarding the importance of serotonin in the fatigue process (Meeusen, Piacentini, Van den Eynde, Magnus, & De Meirleir, 2001; Meeusen, Roeykens, Magnus, Keizer, & De Meirleir, 1997; Pannier, Bouckaert, & Lefebvre, 1995; Strachan, Leiper, & Maughan, 2004).

The neuromuscular and performance effects of acute and long-term exposure to fluoxetine have also been examined (Parise, Bosman, Boecker, Barry, & Tarnopolsky, 2001). Serotonin was demonstrated to alter an individual's sensation of pain; this study differs from many others in this area by investigating whether manipulation of serotonergic neurotransmission could alter the response to high-intensity and resistance exercise. Following periods of acute and chronic (2 weeks) administration, Parise *et al.* concluded that SSRIs do not influence measures of strength or high-intensity exercise performance, including maximum voluntary contractions, voluntary activation percentage, repeated Wingate and high-intensity exercise tests to volitional exhaustion in young adult men.

Catecholaminergic drugs

Because of the complexity of brain functioning and the contradictory results of studies that have tried to manipulate only serotonergic activity, it is unlikely that one single neurotransmitter is responsible for a centrally mediated component of fatigue. In fact, alterations in catecholamines, as well as other excitatory and inhibitory neurotransmitters (glutamate, GABA, and acetylcholine), have been implicated as possible mediators of central fatigue during exercise (Meeusen & De Meirleir, 1995). These neurotransmitters are known to play a role in arousal, mood, motivation, vigilance, anxiety, and reward mechanisms, and could therefore, if adversely affected, impair performance. It is therefore necessary to explore the different transmitter systems and their effect on the neuroendocrine response to endurance exercise.

The neurotransmitters dopamine and noradrenaline have also been linked to the ''central'' component of fatigue, due to their well-known role in motivation and motor behaviour (Davis & Bailey, 1997; Meeusen & De Meirleir, 1995), and are therefore thought to have an enhancing effect on performance. Dopamine and noradrenaline are synthesized through a shared metabolic pathway, with the amino acid tyrosine acting as the precursor. Tyrosine is found in protein-rich dietary sources, including chicken and milk, but unlike tryptophan it is a non-essential LNAA that can also be synthesized from phenylalanine in the liver. Cerebral uptake of tyrosine is subject to competitive transport across the blood–brain barrier by the LNAA-carrier system, which is shared with tryptophan and the other LNAAs as discussed above.

Early pharmacological manipulation of central neurotransmission to improve exercise performance focused largely on the effects of amphetamines, which have a long history of abuse in sport. Amphetamine is a close analogue of dopamine and noradrenaline, and is thought to act directly on catecholaminergic neurones to produce a marked elevation in extracellular dopamine concentrations. This response is believed to be mediated through the stimulation of dopamine release from storage vesicles, inhibition of dopamine reuptake, and the inhibition of dopamine metabolism by monoamineoxidase. Amphetamines may also limit the synthesis of serotonin through a reduction in tryptophan hydroxylase activity and a direct interaction between dopamine release and serotonergic neurotransmission. Studies have demonstrated a clear performance benefit following the administration of amphetamine to both rodents (Gerald, 1978) and humans (Borg, Edstrom, Linderholm, & Marklund, 1972; Chandler & Blair, 1980). The ergogenic action of amphetamine is thought to be mediated through the maintenance of dopamine release late in exercise.

The importance of dopamine in the development of fatigue has been shown in animal studies (Heyes, Garnett, & Coates, 1985; Kalinski, Dluzen, & Stadulis, 2001). It would appear that at the point of fatigue extracellular dopamine concentrations are low, possibly due to the interaction with brain serotonin (Bailey *et al.*, 1992), or a depletion of central catecholamines (Davis & Bailey, 1997). In a series of studies, we supplemented athletes with (1) venlafaxine, a combined serotonin/noradrenaline reuptake inhibitor (SNRI; Piacentini, Meeusen, Buyse, De Schutter, & De Meirleir, 2002a), (2) reboxetine, a noradrenaline reuptake inhibitor (NARI; Piacentini *et al.*, 2002b), and (3) Buproprion, a combined noradrenaline/dopamine reuptake inhibitor (Piacentini, Meeusen, Buyse, De Schutter, & De Meirleir, 2004). Athletes performed two cycle time-trials requiring the completion of a predetermined amount of work as quickly as possible ($\sim$90 min), in a double-blind randomized crossover design. None of the agents above mentioned had a significant influence (either negative or positive) on exercise performance. Each drug clearly altered central neurotransmission, since different neuroendocrine effects were observed depending on the type of reuptake inhibitor administered.

Central fatigue and nutritional interventions

Much of the attraction of the hypothesis described by Newsholme and co-workers (1987) was the potential for nutritional manipulation of neurotransmitter

precursors to delay the onset of central fatigue, potentially enhancing performance. In recent years, a number of studies have attempted to attenuate the increase in central serotonin levels and maintain/increase catecholaminergic neurotransmission through dietary supplementation with specific nutrients, including branched-chain amino acids, tyrosine, and carbohydrate.

Amino acid supplementation

As free tryptophan competes with branched-chain amino acids (BCAA) for transport across the blood–brain barrier into the CNS, reducing the plasma concentration ratio of free tryptophan to BCAA through the provision of exogenous BCAA has been suggested as a practice to attenuate the development of central fatigue. The first research to test the efficacy of BCAA supplementation in attenuating serotonin-mediated fatigue was a field study of the physical and mental performance of male volunteers competing in either a marathon or a 30 km cross-country race (Blomstrand, Hassmen, Ekblom, & Newsholme, 1991a). The results of this study suggested that both physical (race time) and mental (colour and word tests) performance were enhanced in the participants who received BCAA before exercise. However, enhanced performance was witnessed only in participants completing the marathon in times slower than 3 h 5 min, with the lack of a response in the faster runners being attributed to an increased resistance to the feelings associated with central and peripheral fatigue. The reliability of these results has been subsequently questioned, due to a number of methodological problems largely relating to the field-based nature of the study (Davis & Bailey, 1997).

While there is some additional evidence of BCAA ingestion influencing ratings of perceived exertion (RPE; Blomstrand, Hassmen, Ek, Ekblom, & Newsholme, 1997) and mental performance (Blomstrand, Hassmen, & Newsholme, 1991b; Hassmen, Blomstrand, Ekblom, & Newsholme, 1994), the results of several apparently well-controlled laboratory studies have not demonstrated a positive effect on exercise capacity or performance. No ergogenic benefit has been reported during prolonged fixed-intensity exercise to exhaustion (Blomstrand, Andersson, Hassmen, Ekblom, & Newsholme, 1995; Blomstrand *et al.*, 1997; Galiano *et al.*, 1991; Struder *et al.*, 1998; van Hall, Raaymakers, Saris, & Wagenmakers, 1995), prolonged time-trial (TT) performance (Hassmen *et al.*, 1994; Madsen, Kiens, & Christensen,, 1996), or incremental exercice (Varnier *et al.*, 1994). Davis, Welsh, De Volve and Alderson (1999) investigated the effects of BCAA ingestion on the performance of a test specific to the intermittent, high-intensity activity involved in football. The effects of a sugar-free placebo, a carbohydrate solution (CHO), and a carbohydrate solution with added BCAA (CHO+BCAA) on exercise time to exhaustion were examined. Compared with the placebo trial, participants were able to run significantly longer when the CHO and CHO+BCAA solutions were ingested, but the addition of BCAA resulted in no further benefit. The possible influence of carbohydrate ingestion on the development of central fatigue is discussed below, but it is possible that the co-ingestion of BCAA together with carbohydrate may have masked any performance effect.

One possible explanation for a failure to observe an ergogenic effect in many BCAA studies, despite a good rationale for their use, is an increase in ammonia production (Davis & Bailey, 1997). During prolonged intense exercise, the plasma concentration of ammonia increases, with this increase amplified by BCAA ingestion. Since ammonia can readily cross the blood–brain barrier, it may enter the CNS where excessive accumulation may have a profound effect on cerebral function. Evidence suggests that hyperammonaemia has a marked effect of cerebral blood flow, energy metabolism, astrocyte function, synaptic transmission, and the regulation of various neurotransmitter systems (Felipo & Butterworth, 2002). Therefore, it has been considered that exercise-induced hyperammonaemia could also be a mediator of CNS fatigue during prolonged exercise (Davis & Bailey, 1997). Recently, Nybo, Dalsgaard, Steensberg, Moller and Secher (2005) reported that during prolonged exercise the cerebral uptake and accumulation of ammonia may provoke fatigue, through a disturbance to neurotransmitter metabolism. Marked increases in circulating ammonia concentrations have been reported during top-flight football matches (Mohr *et al.*, 2005), thus an accumulation of serum ammonia may contribute to the development of fatigue through disruptions in peripheral and cerebral metabolism.

The flip-side of the serotonin-fatigue hypothesis is the idea that increased catecholaminergic neurotransmission will favour feelings of arousal, motivation, and reward, consequently enhancing exercise performance. In a similar manner to serotonin, central dopamine and noradrenaline synthesis is reliant on the delivery of the non-essential amino acid tyrosine, but the rate of synthesis appears also to be limited by the activity of the catecholaminergic neurons (Davis & Bailey, 1997). Despite a good rationale for its use, evidence of an ergogenic benefit of tyrosine supplementation during prolonged exercise is limited. Work by Struder and colleagues (1998) failed to observe any change in the capacity to perform prolonged exercise following the ingestion of tyrosine immediately before (10 g) and during exercise (10 g). It has been suggested that the high dose of tyrosine administered in this study may have resulted in an inhibition of dopamine synthesis, but a recent report administering

half the dose employed by Struder *et al.* (1998) also found no effect on time-trial performance (Chinevere, Sawyer, Creer, Conlee, & Parcell, 2002). Additionally, oral ingestion of tyrosine by humans had no measurable effect on endurance, muscle strength, or anaerobic power (Sutton, Coll, & Deuster, 2005).

While evidence for an effect of tyrosine on physical performance is limited, stress-related decrements in mood and task performance are reported to be reduced by tyrosine supplementation during sustained military operations exceeding 12 h, involving severe sleep deprivation and fatigue (Owasoyo, Neri, & Lamberth, 1992). There are also several reports indicating that tyrosine ingestion improves stress-induced cognitive and behavioural deficits, in particular working memory, tracking, and stress-sensitive attentional focus tasks (Banderet & Lieberman, 1989; Deijen, Wientjes, Vullinghs, Cloin, & Langefeld, 1999; Dollins, Krock, Storm, Wurtman, & Lieberman, 1995; Neri *et al.*, 1995; Shurtleff, Thomas, Schrot, Kowalski, & Harford, 1994; Sutton *et al.*, 2005). As football is highly dependent on the successful execution of fine and gross motor skills, the possibility that tyrosine ingestion may attenuate a loss in cognitive function that occurs during the later stages of a game would be desirable, despite no apparent benefit to physical performance. It is yet to be seen whether these results can be reproduced in a football-specific protocol.

Carbohydrate supplementation

Analysis of the activity patterns and muscle biopsy data taken from football players suggest that there is a large reliance on carbohydrate utilization, and ingestion of exogenous carbohydrate before and during matches has been reported to enhance performance during the latter stages of a game (Kirkendall, 1993). The peripheral effects of carbohydrate ingestion will be discussed elsewhere in this issue, but it is clear that the provision of exogenous carbohydrate during exercise can also have a profound effect on the CNS.

Carbohydrate feeding suppresses lipolysis, consequently lowering the circulating concentration of plasma free fatty acids. Recognizing this, Davis *et al.* (1992) suggested carbohydrate ingestion as a means of reducing cerebral tryptophan uptake. A five- to sevenfold increase in the plasma concentration ratio of free tryptophan to BCAA was reported under placebo conditions. Supplementation with a 6% or 12% carbohydrate solution attenuated the increase in plasma free fatty acids and free tryptophan, reducing the plasma concentration ratio of free tryptophan to BCAA in a dose-dependent manner. Exercise capacity in the carbohydrate trials was increased compared with placebo, suggesting carbohydrate ingestion as an effective means of delaying the onset of central fatigue; however, it is difficult to separate the contribution of central factors from the widely reported benefits of carbohydrate at attenuating peripheral fatigue.

Several studies have directly examined the effect of carbohydrate supplementation on the development of fatigue during team sport-based activity (Davis *et al.*, 1999; Nicholas, Williams, Lakomy, Phillips, & Nowitz, 1995; Welsh, Davis, Burke, & Williams, 2002; Winnick *et al.*, 2005). It is clear that carbohydrate ingestion can have a profound effect on measures of physical fatigue during this type of exercise, with marked improvements in time to volitional exhaustion, maintenance of sprint performance, and vertical jump height. Recent work has also focused on the effects of carbohydrate supplementation on measures of CNS fatigue, assessed largely through the performance of skills-based tasks and psychological inventories. Ingestion of carbohydrate before and during exercise has been reported to attenuate decrements in performance of whole-body motor skills tasks (Welsh *et al.*, 2002; Winnick *et al.*, 2005).

The beneficial effect of carbohydrate supplementation during prolonged exercise could also relate to increased (or maintained) substrate delivery for the brain, with a number of studies indicating that hypoglycaemia affects brain function and cognitive performance. Exercise-induced hypoglycaemia has been reported to reduce brain glucose uptake and overall cerebral metabolic rate (Nybo, Moller, Pedersen, Nielsen, & Secher, 2003), which is associated with a marked reduction in voluntary activation during sustained muscular contractions (Nybo, 2003). The reduction in CNS activation is abolished when euglycaemia was maintained. Ingestion of carbohydrate has also been reported to minimize the negative effect of prolonged exercise on cognitive function, with an improvement in the performance of complex cognitive tasks observed following running (Collardeau *et al.*, 2001). The results of animal studies suggest that glucose plays an important role in the regulation of central neurotransmission and alterations in extracellular glucose concentrations have been demonstrated to influence serotonin release and reuptake during exercise and recovery (Bequet, Gomez-Merino, Berthelot, & Guezennec, 2002). In addition to changes in circulating blood glucose, the possibility that the depletion of brain glycogen may be important to the development of fatigue during strenuous exercise has recently been explored (Dalsgaard, Ide, Cai, Quistorff, & Secher, 2002).

What other factors might be responsible for 'central fatigue'?

Fatigue – and "central fatigue" in particular – is a complex and multifaceted phenomenon. There are

several other possible cerebral factors that might limit exercise performance, all of which influence signal transduction, since the brain cells communicate through chemical substances. Not all of these relationships have been explored in detail, and the complexity of brain neurochemical interactions makes it difficult to construct a single or simple statement that covers the "central fatigue" phenomenon. Other neurotransmitters such as acetylcholine, GABA, and glutamate have been suggested to be involved to a lesser extent in the development of central fatigue (Abdelmalki, Merino, Bonneau, Bigard, & Guezennec, 1997; Conlay, Sabounjian, & Wurtman, 1992) and as such will not be discussed in this review. Attention has also been given to the influence of ammonia on cerebral levels of glutamate, glutamine, and GABA (Davis & Bailey, 1997; Nybo *et al.*, 2005).

In recent years, the role of central adenosine has been investigated, through its association with caffeine (Davis *et al.*, 2003). The ergogenic effect of caffeine was originally thought to be mediated through an increase in fat oxidation rate, thus sparing muscle glycogen (Costill, Dalsky, & Fink, 1978). Subsequent work has largely failed to provide convincing support for this mechanism, leading to the suggestion that the effects of caffeine supplementation are centrally mediated. Caffeine is a potent adenosine antagonist that readily crosses the blood–brain barrier, producing a marked reduction in central adenosine neurotransmission. Adenosine inhibits the release of many excitatory neurotransmitters, including dopamine and noradrenaline, consequently reducing arousal and spontaneous behavioural activity. The central effects of caffeine have recently been demonstrated by Davis and colleagues (2003), with a marked increase in exercise capacity observed following an infusion of caffeine into the brain of rodents. The influence of caffeine ingestion on both physical and mental performance is discussed by Hespel, Maughan and Greenhaff (2006).

One area of the CNS that has received little attention in relation to exercise is the blood–brain barrier, and the possibility that changes in its integrity may be involved in the fatigue process. The relative impermeability of the blood–brain barrier helps to maintain a stable environment for the brain by regulating exchange between the CNS and the extra-cerebral environment. While the blood–brain barrier is largely resistant to changes in permeability, there are circumstances in which the function of the blood–brain barrier may be either acutely or chronically compromised, with changes potentially resulting in a disturbance of a wide range of homeostatic mechanisms. There is some evidence that prolonged exercise may lead to increased blood–brain barrier permeability in both rodents (Sharma, Westman, Navarro, Dey, & Nyberg, 1996) and humans (Watson, Shirreffs, & Maughan, 2005b). A recent human study reported an increase in circulating serum S100β, a proposed peripheral marker of blood–brain barrier permeability, following prolonged exercise in a warm environment. This response was not apparent following exercise in temperate conditions (Watson *et al.*, 2005b). A similar increase in serum S100β has been reported following football drills involving the repeated heading of a football (Mussack, Dvorak, Graf-Baumann, & Jochum, 2003; Stalnacke, Tegner, & Sojka, 2004), although the authors of these studies perhaps incorrectly interpreted this change as an indication of neuronal damage. Serum S100β is now being employed as an index of brain trauma in individuals who suffer head injuries during sports. Changes in the permeability of the blood – brain barrier to this protein may give misleading results in exercising individuals, particularly under conditions that lead to significant heat stress. At present, the functional consequences of changes in blood–brain barrier permeability during exercise and whether nutritional supplementation can alter this response are not clear.

Other cerebral metabolic, thermodynamic, circulatory, and humoral responses could all lead to a disturbance of cerebral homeostasis and eventually central fatigue. To date there is evidence that because of the extreme disturbance of homeostasis that occurs during prolonged exercise, peripheral and central regulatory mechanisms will be stressed. However, for the moment it is not possible to determine the exact regulation and the importance of each factor.

Hyperthermia, fatigue, and central neurotransmission

The capacity to perform prolonged exercise is clearly impaired in high ambient temperatures (Galloway & Maughan, 1997; Parkin, Carey, Zhao, & Febbraio, 1999). While exercise capacity is thought to be primarily limited by thermoregulatory and fluid balance factors (Hargreaves & Febbraio, 1998), it has been suggested that the CNS may become important in the development of fatigue when body temperature is significantly elevated (Nielsen, 1992). During prolonged exercise in the heat, exhaustion in trained individuals appears to coincide with the attainment of an internal body temperature of around 40.0°C (Gonzalez-Alonso *et al.*, 1999; Nielsen *et al.*, 1993). Hyperthermia has been proposed to accelerate the development of central fatigue during exercise, resulting in a reduction in maximal muscle activation (Nybo & Nielsen, 2001a), altered EEG brain activity (Nielsen, Hyldig, Bidstrup, Gonzalez-Alonso, & Christoffersen, 2001), and increased perceived exertion (Nybo & Nielsen,

2001b). It is likely that this serves as a protective mechanism limiting further heat production when body temperature reaches values that may be detrimental to the organism as a whole, but the neurobiological mechanisms for these responses are not clear at present.

The suggestion that serotonin-mediated fatigue is important during exercise in the heat is partially supported by the work of Mittleman and colleagues (1998). A 14% increase in time to exhaustion in warm ambient conditions (34.4°C) was reported following BCAA supplementation when compared to a polydextrose placebo, with no apparent difference in peripheral markers of fatigue between trials. The authors concluded that the supplementation regimen was successful in limiting the entry of tryptophan into the CNS, attenuating serotonin-mediated fatigue. It is important to note that core temperature at fatigue was significantly below values described as limiting (<38°C). Two subsequent studies have examined the effects of BCAA supplementation on human performance and thermoregulation in the heat (Cheuvront *et al.*, 2004; Watson, Shirreffs, & Maughan, 2004). Cheuvront *et al.* (2004) reported that BCAA, when combined with carbohydrate, did not alter time-trial performance, cognitive performance, mood, ratings of perceived exertion (RPE), thermal comfort, or rectal temperature in the heat when participants were hypohydrated. In this study, hypohydration was used to increase plasma osmolality and increase thermoregulatory and cardiovascular strain. Additionally, ingestion of BCAA solution before, and during, prolonged exercise in glycogen-depleted individuals did not influence exercise capacity, rectal and skin temperature, heart rate, RPE, or perceived thermal stress despite a four-fold reduction in the plasma concentration ratio of free tryptophan to BCAA (Watson *et al.*, 2004).

To date, there has been limited investigation of the influence of pharmacological agents acting on the CNS on the response to prolonged exercise in a warm environment. A recent series of studies examined the effects of acute serotonin (5-HT) agonist (paroxetine) and 5-HT_{2C} receptor antagonist (pizotifen) administration (Strachan, Leiper, & Maughan, 2004, 2005). Neither treatment influenced exercise performance, but pizotifen did produce a marked elevation in core temperature at rest and during exercise, suggesting a role for the 5-HT_{2C} receptor in the regulation of core temperature.

As dopamine and noradrenaline have been implicated in arousal, motivation, reinforcement and reward, the control of motor behaviour and mechanisms of addiction, we recently explored the possible interaction between high ambient temperature and possible underlying neurotransmitter drive during exercise using a dual dopamine/noradrenaline reuptake inhibitor (Watson *et al.*, 2005a). Participants ingested either a placebo or bupropion (Zyban) before exercise in temperate (18°C) or warm (30°C) conditions. Two important findings arose from this study. First, the participants completed a pre-loaded time-trial 9% faster when bupropion was taken before exercise in a warm environment than a placebo. This ergogenic effect was not apparent at 18°C. Second, seven of the nine participants in the heat attained core temperatures equal to, or greater than, 40°C in the bupropion trial, compared to only two participants in the placebo trial.

It is possible that this drug may dampen or override inhibitory signals arising from the CNS to cease exercise due to hyperthermia, and enable an individual to continue to maintain a high power output. It is important to note, however, that this response appeared to occur with the same perception of effort and thermal stress reported during the placebo trial, and may potentially increase the risk of developing heat illness. As evidence for a role of serotonin during exercise in the heat is limited (Cheuvront *et al.*, 2004; Strachan *et al.*, 2004; Watson *et al.*, 2004), these data suggest that catecholaminergic neurotransmission may act as an important neurobiological mediator of fatigue under conditions of heat stress.

It appears that when exercise is performed in high ambient temperatures, the development of central fatigue appears to be accelerated, leading to a loss of drive to continue. This may explain why individuals tend to cease exercise long before muscle glycogen stores reach levels thought to be limiting (Parkin *et al.*, 1999). Until recently, few studies had focused directly on the relationship between brain neurotransmission, thermoregulation, and exercise performance/exercise capacity in a warm environment. Therefore, further research, including both pharmacological and nutritional manipulation, are necessary to elucidate the role of specific neurotransmitter functions during exercise in the heat. Additionally, the significance of this in relation to the pattern of activity associated with football has yet to be determined.

Conclusions

The cause of fatigue is complex, influenced by both events occurring in the periphery and the CNS. The ''central fatigue hypothesis'' is based on the assumption that the synthesis and metabolism of central monoamines are influenced during prolonged exercise, consequently affecting subjective sensations of lethargy and tiredness, causing an altered sensation of effort, perhaps a differing tolerance of pain/discomfort, and a loss of drive and motivation to continue exercise. Since its conception, Newsholme's

original hypothesis has been developed to include the possibility that other neurotransmitters and neuromodulators, in particular the catecholamines, dopamine, and noradrenaline, are also involved in the development of fatigue. Much of the attraction of neurotransmitter-mediated fatigue was the potential for nutritional manipulation of neurotransmitter precursors to delay the onset of central fatigue, potentially enhancing performance.

When exercise is performed in temperate conditions, it seems that manipulation of brain neurotransmission through amino acid supplementation or pharmacological means has little effect (either negatively or positively) on physical performance. While there is some evidence that branched-chain amino acid and tyrosine ingestion can influence perceived exertion and various measures of mental performance (e.g. memory, tracking, cognitive function), the results of several apparently well-controlled laboratory studies have not demonstrated a positive effect on exercise capacity or performance. As football is highly dependent on the successful execution of motor skills and tactics, the possibility that amino acid ingestion may attenuate the loss in cognitive function that occurs during the later stages of a game would be desirable, despite no apparent benefit to physical performance.

It is clear that carbohydrate ingestion can have a profound effect on measures of physical fatigue during high-intensity intermittent activity, with marked improvements in time to volitional exhaustion, maintenance of sprint performance, and vertical jump height. The beneficial effect of carbohydrate supplementation during prolonged exercise may also relate to increased (or maintained) substrate delivery for the brain. Several studies have indicated that hypoglycaemia affects brain function and cognitive performance. There are indications that carbohydrate intake during exercise minimizes the negative effect of central fatigue induced by prolonged exercise on cognitive function.

Although these largely inconsistent findings make it difficult to reach a firm conclusion regarding the role of central neurotransmission in the fatigue process, it is premature to discount its importance in the light of studies investigating amphetamines and other CNS stimulants. Additionally, evidence for a central component of fatigue during prolonged exercise in a warm environment appears to be convincing, with hyperthermia demonstrated to reduce maximal muscle activation, alter brain activity, and increase perceived exertion. To date there has been limited investigation of the influence of nutritional or pharmacological manipulation of central neurotransmission on the response to exercise in a warm environment, and further research in this area is warranted.

Fatigue – and ''central fatigue'' in particular – is a complex and multifaceted phenomenon. There are several other possible cerebral factors that might limit exercise performance, all of which influence signal transduction, since the brain cells communicate through chemical substances. Not all of these relationships have been explored in detail, and the complexity of brain neurochemical interactions will probably make it very difficult to construct a single or simple statement that covers the phenomenon we call ''central fatigue''.

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